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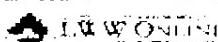
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1: Pancreas 2001 Oct;23(3):251-258

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Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand and Its Receptor Expression and the Pathway of Apoptosis in Human Pancreatic Cancer.

Satoh K, Kaneko K, Hirota M, Masamune A, Satoh A, Shimosegawa T.

Department of Gastroenterology, Division of Internal Medicine, Tohoku University Graduate School of Medicine, Seiryō-machi, Aobaku, Sendai, Japan.

METHODOLOGY: The authors performed the reverse transcription-polymerase chain reaction (RT-PCR) in 17 cases of pancreatic ductal cell carcinoma (PDC) and five cases of normal pancreatic tissues to determine the expression of tumor necrosis factor - related apoptosis-inducing factor (TRAIL) and its five receptors in PDC. **RESULTS:** The expression of TRAIL and its receptors other than osteoprotegerin was found frequently in both PDC and normal tissues, whereas the expression of osteoprotegerin was detected only in PDC. The authors detected cancer cell death by TRAIL, ranging from 37% to 77% in all the PDC cell lines by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Highest staining revealed that cell death was caused by apoptosis. Caspase-8 and caspase-3 and poly (ADP-ribose) polymerase cleavage was activated within 2 hours after stimulation with 200 ng/mL TRAIL. **CONCLUSION:** These findings suggest a relation between osteoprotegerin expression and the biologic aggressiveness of PDC and the involvement of caspase-8 and caspase-3 activation in the TRAIL-mediated apoptosis pathway in PDC.

PMID: 11590320 [PubMed - as supplied by publisher]

2: Am J Kidney Dis 2001 Oct;38(4 Suppl 1):S175-7

Related Articles, Books, LinkOut

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Osteoprotegerin levels before and after renal transplantation.

Sato T, Tominaga Y, Iwasaki Y, Kazama JJ, Shigematsu T, Inagaki H, Watanabe I, Katayama A, Haba T, Uchida K, Fukagawa M.

Department of Transplant Surgery, Nagoya 2nd Red Cross Hospital, Nagoya, Japan.
tetsu.sato@nagoya2.jrc.or.jp

Osteoprotegerin (OPG) is a newly identified glycoprotein that belongs to the tumor necrosis factor receptor superfamily and regulates bone mass by inhibiting osteoclastic bone resorption. The regulatory mechanism of OPG is still unclear after successful renal transplantation (RTX), however, resulting in resolution of uremia. The present study was designed to clarify the potential role of OPG in uremia and after RTX under immunosuppressive therapy. We evaluated circulating OPG levels by measuring them

before and after RTX (postoperative days 2, 14, and 28). Our protocol of immunosuppressive drugs was dual therapy using cyclosporine and steroids. Serum OPG was quantitated using enzyme-linked immunosorbent assay. After successful RTX, serum OPG levels decreased significantly on day 14 and day 28 compared with the baseline level ($P < 0.05$). Creatinine clearance dramatically increased until day 14 and decreased thereafter. Serum OPG declines for the first 2 weeks after RTX owing to functioning allograft and decreases again for the next 2 weeks because of steroids and possible immunosuppressive agents.

PMID: 11576949 [PubMed - in process]

3: Blood 2001 Oct 1;98(7):2269-71

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Serum osteoprotegerin levels are reduced in patients with multiple myeloma with lytic bone disease.

Seidel C, Hjertner O, Abildgaard N, Heickendorff L, Hjorth M, Westin J, Nielsen JL, Hjorth-Hansen H, Waage A, Sundan A, Borset M; Nordic Myeloma Study Group.

Institute of Cancer Research and Molecular Biology, and the Section of Hematology, Department of Internal Medicine, University Hospital, Norwegian University of Science and Technology, Trondheim, Norway.

Osteoprotegerin (OPG), the neutralizing decoy receptor for the osteoclast activator RANK ligand, was measured in serum taken from patients with multiple myeloma at the time of diagnosis. Median OPG was lower in the patients with myeloma (7.4 ng/mL; range, 2.6-80; $n = 225$) than in healthy age- and sex-matched controls (9.0 ng/mL; range 5.1-130; $n = 40$; $P = .02$). Importantly, OPG levels were associated with degree of radiographically assessed skeletal destruction ($P = .01$). The median OPG level in patients lacking osteolytic lesions was 9.1 ng/mL, as compared with 7.6 ng/mL and 7.0 ng/mL, respectively, in patients with minor or advanced osteolytic disease. Furthermore, OPG levels were associated with World Health Organization performance status ($P = .003$) and correlated to serum levels of carboxy-terminal propeptide of type I procollagen (PICP; $P < .001$) but not with clinical stage or survival. These findings suggest impaired OPG function in myeloma and give a rationale for OPG as a therapeutic agent against myeloma bone disease.

PMID: 11568016 [PubMed - in process]

4: Proc Natl Acad Sci U S A 2001 Sep 25;98(20):11581-6

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Multiple myeloma disrupts the TRANCE/ osteoprotegerin cytokine axis to trigger bone destruction and promote tumor progression.

Pearse RN, Sordillo EM, Yaccoby S, Wong BR, Liau DF, Colman N, Michaeli J, Epstein J, Choi Y.

Laboratories of Molecular Genetics and Immunology, and Howard Hughes Medical Institute, The Rockefeller University, New York, NY 10021, USA.
rmp2001@med.cornell.edu

Bone destruction, caused by aberrant production and activation of osteoclasts, is a prominent feature of multiple myeloma. We demonstrate that myeloma stimulates osteoclastogenesis by triggering a coordinated increase in the tumor necrosis factor-related activation-induced cytokine (TRANCE) and decrease in its decoy receptor, osteoprotegerin (OPG). Immunohistochemistry and *in situ* hybridization studies of bone

marrow specimens indicate that *in vivo*, deregulation of the TRANCE-OPG cytokine axis occurs in myeloma, but not in the limited plasma cell disorder monoclonal gammopathy of unknown significance or in nonmyeloma hematologic malignancies. In coculture, myeloma cell lines stimulate expression of TRANCE and inhibit expression of OPG by stromal cells. Osteoclastogenesis, the functional consequence of increased TRANCE expression, is counteracted by addition of a recombinant TRANCE inhibitor, RANK-Fc, to marrow/myeloma cocultures. Myeloma-stroma interaction also has been postulated to support progression of the malignant clone. In the SCID-hu murine model of human myeloma, administration of RANK-Fc both prevents myeloma-induced bone destruction and interferes with myeloma progression. Our data identify TRANCE and OPG as key cytokines whose deregulation promotes bone destruction and supports myeloma growth.

PMID: 11562486 [PubMed - in process]

5: Endocrinology 2001 Sep;142(9):4047-54

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Catabolic effects of continuous human PTH (1–38) *in vivo* is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation.

Ma YL, Cain RL, Halladay DL, Yang X, Zeng Q, Miles RR, Chandrasekhar S, Martin TJ, Onyia JE.

Gene Regulation, Bone and Inflammation Research Division, Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, Indiana 46285, USA. ma_linda@lilly.com

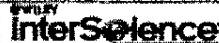
Continuous infusion of PTH *in vivo* results in active bone resorption. To investigate the molecular basis of the catabolic effect of PTH *in vivo*, we evaluated the role of OPG and RANKL, which are known to influence osteoclast formation and function.

Weanling rats fed a calcium-free diet were parathyroidectomized and infused with PTH via an Alzet pump to examine: 1) the changes of serum-ionized calcium and osteoclast number, 2) the expression of OPG/RANKL mRNA and protein, and 3) the expression of osteoblast phenotype bone formation-associated genes such as osteoblast specific transcription factor, osteocalcin, bone sialoprotein, and type I collagen. PTH (1–38) (0.01–20 microg/100 g) continuous infusion for 1–24 h resulted in a dose-dependent increase in serum-ionized calcium in parathyroidectomized rats and a corresponding dose-dependent increase in osteoclast number, indicating an increased bone resorption. At 20 microg/100 g PTH dose level, serum-ionized calcium was 2.1-fold of the vehicle control and not different from the Sham-parathyroidectomized rats, and osteoclast number was 3-fold of the vehicle control and 1.7-fold of the Sham-parathyroidectomized rats. In the distal femur, RANKL mRNA expression was increased (27-fold) and OPG mRNA expression was decreased (4.6-fold). The changes in RANKL and OPG mRNA levels were rapid (as early as 1 h), dose dependent, and sustained over a 24-h period that was examined. Immunohistochemical evaluation of bone sections confirmed that OPG level was reduced in proximal tibial metaphysis upon PTH infusion. Circulating OPG protein level was also decreased by 32% when compared with the parathyroidectomized control. The expression of genes that mark the osteoblast phenotype was significantly decreased [osteoblast specific transcription factor (2.3-fold), osteocalcin (3-fold), bone sialoprotein (2.8-fold), and type I collagen (5-fold)]. These results suggest that the catabolic effect of PTH infusion *in vivo* in this well-established resorption model is associated with a reciprocal expression of OPG/RANKL and a co-ordinate decrease in the expression of bone formation-related genes. We propose that the rapid and sustained increase in RANKL and decrease in OPG initiate maintain and favor the cascade of events in the differentiation/recruitment and activation of osteoclasts.

PMID: 11517184 [PubMed - indexed for MEDLINE]

6: Cancer 2001 Aug 1;92(3):460-70

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Receptor activator of nuclear factor-kappaB ligand and osteoprotegerin: potential implications for the pathogenesis and treatment of malignant bone diseases.

Hofbauer LC, Neubauer A, Heufelder AE.

Division of Gastroenterology, Endocrinology and Metabolism, Department of Medicine, Philipps University, Baldingerstrasse, D-35033 Marburg, Germany.
hofbauer@post.med.uni-marburg.de

BACKGROUND: The current review summarizes the roles of the ligand, receptor activator of nuclear factor-kappaB ligand (RANKL), its receptor, receptor activator of nuclear factor-kappaB (RANK), and its decoy receptor, osteoprotegerin (OPG), on osteoclast biology and bone resorption. Furthermore, it highlights the impact of these compounds on the pathogenesis of malignant bone diseases, including tumor metastasis, humoral hypercalcemia of malignancy, and multiple myeloma. Finally, the authors discuss the therapeutic potential of OPG in the management of malignancies involving the skeleton. **METHODS:** After its discovery and cloning, the biologic effects of RANKL, RANK, and OPG have been characterized by *in vitro* experiments and *in vivo* studies. The generation of knock-out mice and transgenic mice has produced animal models with absent or excessive production of these cytokine components that display opposite abnormal skeletal phenotypes (osteoporosis or osteopetrosis). The potential effect of RANKL and OPG has been assessed by evaluating these compounds in various animal models of metabolic and malignant bone disease and by administering OPG to humans. **RESULTS:** Abnormal bone resorption due to local or systemic stimulation of osteoclast differentiation and activation is a hallmark of various benign and malignant bone diseases. RANKL, RANK, and OPG form an essential cytokine system that is capable of regulating all aspects of osteoclast functions, including proliferation, differentiation, fusion, activation, and apoptosis. The balance of bone resorption depends on the local RANKL-to-OPG ratio, which is enhanced in bone metastases and humoral hypercalcemia of malignancy. The exogenous administration of OPG to tumor-bearing animals corrects the increased RANKL-to-OPG ratio, and reverses the skeletal complications of malignancies. **CONCLUSIONS:** Abnormalities of the RANKL/OPG system have been implicated in the pathogenesis of various primary and secondary bone malignancies. The systemic administration of OPG appears to be a potent novel therapeutic agent for treatment of these disorders. Copyright 2001 American Cancer Society.

Publication Types:

- Review
- Review, academic

PMID: 11505389 [PubMed - indexed for MEDLINE]

7: J Bone Miner Res 2001 Aug;16(8):1416-25

Books, LinkOut

Expression profiles of receptor activator of nuclear factor kappaB ligand, receptor activator of nuclear factor kappaB, and osteoprotegerin messenger RNA in aged and ovariectomized rat bones.

Ikeda T, Utsuyama M, Hirokawa K.

Department of Pathology and Immunology, Aging and Developmental Science, Graduate School, Tokyo Medical and Dental University, Japan.

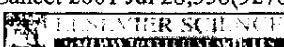
The receptor activator of nuclear factor-kappaB ligand (RANKL; also known as tumor necrosis factor-related activation-induced cytokine [TRANCE], osteoprotegerin ligand [OPGL], and osteoclast differentiation factor [ODF]) is a transmembrane ligand expressed in osteoblasts and bone marrow stromal cells. It binds to RANK, which is expressed in osteoclast progenitor cells, and induces osteoclastogenesis. OPG, a decoy

receptor for RANKL, also binds to RANKL, and competitive binding of RANKL with RANK or OPG is thought to regulate bone metabolism. To investigate roles of the RANKL/RANK/OPG system in pathophysiological conditions, the expression of RANKL, RANK, and OPG messenger RNA (mRNA) was analyzed in bones of aged and ovariectomized rats by means of *in situ* hybridization. In the control 8-week-old male and sham-operated female rat bones, the expression of RANKL mRNA was detected in hypertrophic chondrocytes of the growth plate and some periosteal and endosteal mesenchymal cells. The expression of RANK mRNA was detected in osteoclast-like cells and mononuclear cells in contact with the cortical and trabecular bones. The expression of OPG mRNA was detected in proliferating chondrocytes and osteocytes. In the 2.5-year-old rat bones, the expression of RANKL, RANK, and OPG mRNA tended to decrease except for the endosteal region. In the ovariectomized rat bones, the expression of RANKL, RANK, and OPG mRNA increased, and high expression of OPG mRNA was induced in resting chondrocytes and osteocytes. These results suggest that estrogen deficiency stimulates the RANKL/RANK/OPG system and induces OPG in cells that have been thought to be less important for bone metabolism.

PMID: 11499864 [PubMed - in process]

8: Lancet 2001 Jul 28;358(9278):257-9

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Osteoprotegerin: a link between osteoporosis and arterial calcification?

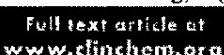
Hofbauer LC, Schoppe M.

Division of Gastroenterology and Endocrinology, Philipps-University, D-35033, Marburg, Germany. hofbauer@post.med.uni-marburg.de

PMID: 11498208 [PubMed - indexed for MEDLINE]

9: Clin Chem 2001 Aug;47(8):1475-7

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Immuno-PCR assay for homodimeric osteoprotegerin.

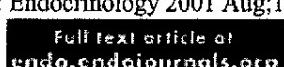
Furuya D, Kaneko R, Yagihashi A, Endoh T, Yajima T, Kobayashi D, Yano K, Tsuda E, Watanabe N.

Division of Laboratory Diagnosis, Sapporo Medical University School of Medicine, Sapporo 060-8543, Japan.

PMID: 11468243 [PubMed - indexed for MEDLINE]

10: Endocrinology 2001 Aug;142(8):3546-53

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Leptin reduces ovariectomy-induced bone loss in rats.

Burguera B, Hofbauer LC, Thomas T, Gori F, Evans GL, Khosla S, Riggs BL, Turner RT.

Division of Endocrinology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15261, USA. burguerab@msx.dept-med.pitt.edu

Bone mineral density increases with fat body mass, and obesity has a protective effect

against osteoporosis. However, the relationship between fat body mass and bone mineral density is only partially explained by a combination of hormonal and mechanical factors. Serum leptin levels are strongly and directly related to fat body mass. We report here the effects of leptin administration compared with estrogen therapy on ovariectomy-induced bone loss in rats. Leptin was effective at reducing trabecular bone loss, trabecular architectural changes, and periosteal bone formation. Interestingly, the combination of estrogen and leptin further decreased bone turnover compared with that in estrogen-treated ovariectomized rats. Leptin also significantly increased osteoprotegerin mRNA steady state levels and protein secretion and decreased RANK ligand mRNA levels in human marrow stromal cells in vitro. Our findings suggest that leptin could modulate bone remodeling in favor of a better bone balance in rats. This study is the first evidence that leptin therapy has a significant effect in preventing ovariectomy-induced bone loss, and this effect may at least in part be mediated by the osteoprotegerin/RANK ligand pathway.

PMID: 11459801 [PubMed - indexed for MEDLINE]

11: Eur J Endocrinol 2001 Aug;145(2):199-205

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Serum parathyroid hormone, but not menopausal status, is associated with the expression of osteoprotegerin and RANKL mRNA in human bone samples.

Seck T, Diel I, Bismar H, Ziegler R, Pfeilschifter J.

Department of Internal Medicine I, University of Heidelberg, 69115 Heidelberg, Germany. Thomas.Seck@yale.edu

OBJECTIVE: Osteoprotegerin (OPG) and its ligand 'receptor activator of NF- κ B ligand' (RANKL) are important regulators of bone metabolism. RANKL, expressed in osteoblasts, activates osteoclast differentiation and osteoclast function by binding the 'receptor activator of NF- κ B' (RANK), expressed in osteoclast precursors and mature osteoclasts. The effect is prevented by OPG, a soluble receptor of RANKL. In vitro studies have suggested that estrogen stimulates OPG, whereas parathyroid hormone (PTH) inhibits OPG expression and stimulates the expression of RANKL. **DESIGN:** In the present study, we examined the relationship between the menopause, serum PTH and the expression of OPG and RANKL in human bone tissue *in vivo*. **METHODS:** To address this question, we established a 5'-nuclease assay to quantify the mRNA copies of human OPG and RANKL, normalized to the number of copies of beta-actin mRNA in 169 women (mean age: 52.4 \pm 11.6 years), who underwent surgery for early breast cancer. Intact serum PTH was measured by chemoluminescence in 61 women.

RESULTS: We found no significant difference in the expression of OPG and RANKL between postmenopausal women and premenopausal women. Also, the ratio of RANKL to OPG was unchanged in relation to the menopausal status. Serum PTH was negatively associated with the expression of OPG ($r=-0.33$, $P=0.01$), but also, surprisingly, with the expression of RANKL ($r=-0.28$, $P=0.03$). **CONCLUSION:** We failed to observe the expected changes in the expression of OPG and RANKL in human bone samples at menopause. High *in vivo* levels of circulating PTH are accompanied by low levels of expression of the two transcripts in human bone tissue.

PMID: 11454517 [PubMed - indexed for MEDLINE]

12: J Biol Chem 2001 Sep 28;276(39):36241-50

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Stimulation of osteoprotegerin (opg) gene expression by transforming growth factor-beta (tgf-beta). mapping of the opg promoter region that mediates tgf-beta effects.

Thirunavukkarasu K, Miles RR, Halladay DL, Yang X, Galvin RJ, Chandrasekhar S, Martin TJ, Onyia JE.

Gene Regulation, Bone and Inflammation Research, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana 46285 and St. Vincent's Institute for Medical Research, Fitzroy, Victoria 3065, Australia.

Transforming growth factor-beta (TGF-beta) regulates osteoclastogenesis and osteoclast survival, in part through the induction of osteoprotegerin (OPG), a protein known to inhibit osteoclast formation and function. To explore the molecular basis of TGF-beta regulation of OPG expression, we evaluated the effects of TGF-beta on osteoclast formation, OPG protein secretion, mRNA expression, and gene transcription. The marked inhibitory effect of TGF-beta on osteoclast differentiation was confirmed in a co-culture model utilizing murine stromal/osteoblastic BALC cells and bone marrow hematopoietic precursors. This inhibition in osteoclast differentiation was preceded by a decrease in RANKL mRNA expression (5-fold) and a reciprocal increase in OPG mRNA (6.1-fold) and protein (7.1-fold) expression in BALC cells. At the promoter/transcriptional level, TGF-beta treatment resulted in a 3-10-fold increase in reporter gene activity directed by a 5.9-kilobase fragment of the human OPG promoter in transfection assays performed in UMR106 cells. The effect of TGF-beta was mimicked by TGF-beta2 and -beta3 but not by BMP-4, suggesting a TGF-beta signal-specific effect. Deletion analysis revealed that a 183-base pair region (-372 to -190) in the promoter was required for TGF-beta responsiveness, and this region was sufficient to confer TGF-beta inducibility to a heterologous (osteocalcin) minimal promoter. Substitution mutations that disrupted the Cbfa1- and/or Smad-binding elements present in the 183-base pair region resulted in a decrease in base-line expression and in the responsiveness to TGF-beta and Cbfa1. Collectively, these studies indicate the involvement and possible interaction of Cbfa1 and Smad proteins in mediating the effects of TGF-beta on OPG transcription.

PMID: 11451955 [PubMed - in process]

13: J Clin Endocrinol Metab 2001 Jul;86(7):3162-5

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jcem.endojournals.org

Osteoprotegerin serum levels in men: correlation with age, estrogen, and testosterone status.

Szule P, Hofbauer LC, Heufelder AE, Roth S, Delmas PD.

INSERM, U-403, Hopital Edouard Herriot (P.S., P.D.D.), 69437 Lyon, France.

Previous studies have suggested an important role for androgens and estrogens in bone metabolism in men. However, their local mode of action has not been clearly established. Osteoprotegerin (OPG) is a secreted decoy receptor that inhibits osteoclast formation and activity by neutralizing its cognate ligand. To assess the role of OPG on bone metabolism in men, we conducted a study aimed at evaluating OPG serum levels and their correlation with age, bone mineral density, biochemical markers of bone turnover, and testosterone and estradiol levels in 252 men, aged 19-85 yr. Serum concentrations of OPG increased significantly with age ($r = 0.41$; $P = 0.0001$), and were positively correlated with free testosterone index and free estradiol index ($r = 0.20$; $P < 0.002$ and $r = 0.15$; $P < 0.03$, respectively) after adjustment for age and body weight. Beyond the age of 40 yr, OPG serum concentrations were negatively correlated with urinary excretion of total deoxypyridinoline ($r = -0.20$; $P < 0.01$) and PTH serum levels ($r = -0.23$; $P < 0.01$). In contrast, there was no correlation with biochemical markers of bone formation, 25-hydroxyvitamin D(3) levels, or bone mineral density at any site. Our data reveal that age as well as androgen and estrogen status are significant positive determinants, whereas PTH is a negative determinant, of OPG serum levels in men. These data suggest that OPG may be an important paracrine mediator of bone metabolism in elderly men and highlight the role of estrogens in the homeostasis of the male skeleton.

PMID: 11443182 [PubMed - indexed for MEDLINE]

14: Med Res Rev 2001 Jul;21(4):274-301

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Arterial calcification: a review of mechanisms, animal models, and the prospects for therapy.

Wallin R, Wajih N, Greenwood GT, Sane DC.

Section of Rheumatology, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA.

The causes of arterial calcification are beginning to be elucidated. Macrophages, mast cells, and smooth muscle cells are the primary cells implicated in this process. The roles of a variety of bone-related proteins including bone morphogenetic protein-2 (BMP-2), matrix Gla protein (MGP), osteoprotegerin (OPG), osteopontin, and osteonectin in regulating arterial calcification are reviewed. Animals lacking MGP, OPG, smad6, carbonic anhydrase isoenzyme II, fibrillin-1, and klotho gene product develop varying extents of arterial calcification. Hyperlipidemia, vitamin D, nicotine, and warfarin, alone or in various combinations, produce arterial calcification in animal models. MGP has recently been discovered to be an inhibitor of bone morphogenetic protein-2, the principal osteogenic growth factor. Many of the forces that induce arterial calcification may act by disrupting the essential post-translational modification of MGP, allowing BMP-2 to induce mineralization. MGP requires gamma-carboxylation before it is functional, and this process uses vitamin K as an essential cofactor. Vitamin K deficiency, drugs that act as vitamin K antagonists, and oxidant stress are forces that could prevent the formation of GLA residues on MGP. The potential role of arterial apoptosis in calcification is discussed. Potential therapeutic options to limit the rate of arterial calcification are summarized. Copyright 2001 John Wiley & Sons, Inc.

Publication Types:

- Review
- Review, academic

PMID: 11410932 [PubMed - indexed for MEDLINE]

15: Cancer Res 2001 Jun 1;61(11):4432-6

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Osteoprotegerin inhibits osteolysis and decreases skeletal tumor burden in syngeneic and nude mouse models of experimental bone metastasis.

Morony S, Capparelli C, Sarosi I, Lacey DL, Dunstan CR, Kostenuik PJ.

Department of Pharmacology/Pathology, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA.

Certain malignancies, including breast cancer, frequently metastasize to bone, where the tumor cells induce osteoclasts to locally destroy bone. Osteoprotegerin (OPG), a member of the tumor necrosis factor receptor family, is a negative regulator of osteoclast differentiation, activation, and survival. We tested the ability of recombinant OPG to inhibit tumor-induced osteoclastogenesis, osteolysis, and skeletal tumor burden in two animal models. In a syngeneic model, mouse colon adenocarcinoma (Colon-26) cells were injected into the left ventricle of mice. Treatment with OPG dose-dependently decreased the number and area of radiographically evident lytic bone lesions, which, at the highest dose, were undetectable. Histologically, OPG also decreased skeletal tumor burden and tumor-associated osteoclasts. In a nude mouse model, OPG treatment completely prevented radiographic osteolytic lesions caused by human MDA-MB-231 breast cancer cells. Histologically, OPG decreased skeletal tumor burden by 75% and completely eradicated MDA tumor-associated osteoclasts. In

both models, OPG had no effect on metastatic tumor burden in a panel of soft tissue organs. These data indicate that OPG may be an effective therapy for preventing osteolysis and decreasing skeletal tumor burden in patients with bone metastasis.

PMID: 11389072 [PubMed - indexed for MEDLINE]

16: J Clin Invest 2001 May;107(10):1235-44

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- J Clin Invest. 2001 May;107(10):1219-20

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Osteoprotegerin inhibits prostate cancer-induced osteoclastogenesis and prevents prostate tumor growth in the bone.

Zhang J, Dai J, Qi Y, Lin DL, Smith P, Strayhorn C, Mizokami A, Fu Z, Westman J, Keller ET.

Department of Pathology, School of Medicine, University of Michigan, Ann Arbor, Michigan, USA.

Prostate cancer (CaP) forms osteoblastic skeletal metastases with an underlying osteoclastic component. However, the importance of osteoclastogenesis in the development of CaP skeletal lesions is unknown. In the present study, we demonstrate that CaP cells directly induce osteoclastogenesis from osteoclast precursors in the absence of underlying stroma in vitro. CaP cells produced a soluble form of receptor activator of NF- κ B ligand (RANKL), which accounted for the CaP-mediated osteoclastogenesis. To evaluate for the importance of osteoclastogenesis on CaP tumor development in vivo, CaP cells were injected both intratibially and subcutaneously in the same mice, followed by administration of the decoy receptor for RANKL, osteoprotegerin (OPG). OPG completely prevented the establishment of mixed osteolytic/osteoblastic tibial tumors, as were observed in vehicle-treated animals, but it had no effect on subcutaneous tumor growth. Consistent with the role of osteoclasts in tumor development, osteoclast numbers were elevated at the bone/tumor interface in the vehicle-treated mice compared with the normal values in the OPG-treated mice. Furthermore, OPG had no effect on CaP cell viability, proliferation, or basal apoptotic rate in vitro. These results emphasize the important role that osteoclast activity plays in the establishment of CaP skeletal metastases, including those with an osteoblastic component.

PMID: 11375413 [PubMed - indexed for MEDLINE]

17: J Clin Invest 2001 May;107(10):1219-20

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Osteolysis and cancer.

Goltzman D.

Calcium Research Laboratory, Department of Medicine, McGill University Health Center, and Departments of Medicine and Physiology, McGill University, Montreal, Quebec Canada. david.goltzman@mcgill.ca

Publication Types:

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PMID: 11375409 [PubMed - indexed for MEDLINE]

18: Cancer Res 2001 May 15;61(10):4038-47

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Osteoprotegerin diminishes advanced bone cancer pain.

Luger NM, Honore P, Sabino MA, Schwei MJ, Rogers SD, Mach DB, Clohisy DR, Mantly PW.

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Bone cancer pain most commonly occurs when tumors originating in breast, prostate, or lung metastasize to long bones, spinal vertebrae, and/or pelvis. Primary and metastatic cancers involving bone account for approximately 400,000 new cancer cases per year in the United States alone, and >70% of patients with advanced breast or prostate cancer have skeletal metastases. Whereas pain resulting from bone cancer can dramatically impact an individual's quality of life, very little is known about the mechanisms that generate and maintain this pain. To begin to define the mechanisms that give rise to advanced bone cancer pain, osteolytic 2472 sarcoma cells or media were injected into the intramedullary space of the femur of C3H/HeJ mice, and the injection hole was sealed using dental amalgam, confining the tumor cells to the bone. Twelve days after injection of 2472 tumor cells, animals showed advanced tumor-induced bone destruction of the injected femur, bone cancer pain, and a stereotypic set of neurochemical changes in the spinal cord dorsal horn that receives sensory inputs from the affected femur. Administration of osteoprotegerin, a naturally secreted decoy receptor that inhibits osteoclast maturation and activity and induces osteoclast apoptosis, or vehicle was begun at 12 days, when significant bone destruction had already occurred, and administration was continued daily until day 21. Ongoing pain behaviors, movement-evoked pain behaviors, and bone destruction were assessed on days 10, 12, 14, 17, and 21. The neurochemistry of the spinal cord was evaluated at days 12 and 21. Results indicated that osteoprotegerin treatment halted further bone destruction, reduced ongoing and movement-evoked pain, and reversed several aspects of the neurochemical reorganization of the spinal cord. Thus, even in advanced stages of bone cancer, ongoing osteoclast activity appears to be involved in the generation and maintenance of ongoing and movement-evoked pain. Blockade of ongoing osteoclast activity appears to have the potential to reduce bone cancer pain in patients with advanced tumor-induced bone destruction.

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